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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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Victor Willem Van Beusechem

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HOFFMANN & BARON, LLP
6900 JERICO TURNPIKE
SYOSSET, NY 11791

EXAMINER

LONG, SCOTT

ART UNIT

PAPER NUMBER

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12/02/2010

PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/501,407	Applicant(s) VAN BEUSECHEM ET AL.	
	Examiner SCOTT LONG	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 08 November 2010.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 10,15-17,19-23,26-29 and 32-40 is/are pending in the application.
- 4a) Of the above claim(s) 10,15-17 and 19-23 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 26-29 and 32-40 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The examiner acknowledges receipt of Applicant's Remarks and Claim amendments, filed on 8 November 2010.

Claim Status

Claims 10, 15-17, 19-23, 26-29 and 32-40 are pending. Claims 1-9, 11-14, 18, 24-25, 30-31 and 41 have been cancelled. Claims 10, 15-17, and 19-23 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 26-29 and 32-40 are under current examination.

Priority

This application claims benefit from foreign Application No. EP/02075108.7, filed 14 January 2002 and PCT Application No. PCT/EP03/00340, filed 14 January 2003. The instant application has been granted the benefit date, 14 January 2002, from the application EP/02075108.7.

RESPONSE TO ARGUMENTS

35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Curiel & Xu

Claims 26-35 and 38-40 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US-6,824,771) in view of Xu et al. (Human Gene Therapy. 1997; 8:177-185) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues that the combination of references (1) would not have yielded predictable results and (2) would not have a reasonable expectation of success (Remarks, filed 11/8/2010, page 9, parag.4). The applicant proposes a mechanism of how the claimed adenovirus would behave in tumor cells (Remarks, page 10). The applicant also proposes a mechanism of how the adenovirus suggested by the cited art would behave in tumor cells (Remarks, page 11). After making this comparison, the applicant concludes the adenovirus suggested by the proposed combination of art would not function in the same manner as the claimed adenovirus (Remarks, page 11, parag.3). Accordingly, the applicant concludes that the claimed adenovirus would not have been predictable (Remarks, page 11, parag.4) and the applicant thinks the combination of elements in the cited art would be "ineffective" (page 12, parag.1).

In response to applicant's argument that p53 would be "thought ineffective" in the adenovirus of Curiel, the test for obviousness is not whether the features of a secondary reference may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art. See *In re Keller*, 642 F.2d 413, 208

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USPQ 871 (CCPA 1981). Accordingly, the examiner finds the applicant's argument unpersuasive.

In response to applicant's argument that cited art has a different reason for combining the elements than was devised by the applicant, the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985). Curiel et al. teach a conditionally replicative recombinant adenovirus which (1) has a functional E1B-19k and (2) is E1B-55k-deleted or is E1A-deleted/modified and (3) comprises a therapeutic gene operatively linked to a promoter. Simply substituting one therapeutic gene for another (e.g., substituting p53 for HSV-TK) in an adenovirus shown to be effective in treating cancer would have been obvious to a skilled artisan. The molecular biology required to make this substitution is simple for a skilled molecular biologist. A skilled artisan would have found this simple substitution to be *prima facie* obvious. Accordingly, the examiner finds the applicant's argument unpersuasive.

The examiner points out that the claims are directed to a product, namely a conditionally replicative recombinant adenovirus which (1) has a functional E1B-19k and (2) is E1B-55k-deleted or is E1A-deleted/modified and (3) comprises a therapeutic gene (e.g., p53) operatively linked to a promoter. Nearly all of the structural features of the adenovirus are taught in combination by Curiel, with the exception of the particular therapeutic gene, p53. Therefore, inventive feature of the claimed adenovirus seems to be selection of a particular therapeutic gene. As adenovirus-p53 has been used by

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practitioners of gene therapy for decades, the examiner is not persuaded by the applicant's arguments that the combination of Curiel and Xu would be non-obvious.

Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 26-35 and 38-40 under 35 U.S.C. 103(a) as being unpatentable over Curiel et al. in view of Xu et al.

The examiner reiterates the pending rejection:

Claims 26-35 and 38-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US-6,824,771) in view of Xu et al. (Human Gene Therapy. 1997; 8:177-185).

Claim 26 is directed to a replication competent recombinant adenovirus, being capable to replicate and having lytic capacity in target cells, wherein said target cells are hampered in a p53 dependent apoptosis pathway, wherein the adenovirus is a conditionally replicating adenovirus; wherein the adenovirus genome comprises a coding sequence of at least one mammalian restoring factor functional in restoring the p53 apoptosis pathway in said target cells; wherein said coding sequence is operably linked to one or more expression control sequences functional in said target cells, and whereby said restoring factor induces accelerated cell lysis and/or a faster release of virus progeny when compared to a recombinant adenovirus lacking said coding sequence and wherein the virus genome further comprises a gene selected from a gene encoding the adenovirus E1B-19kDa protein or a functional analog or derivative thereof and a gene encoding the adenovirus E1B-55kDa protein or a functional analog or derivative thereof. The structure of the claimed replication competent recombinant

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adenovirus must have E1B-19kDa protein or E1B-55kDa and must have mammalian p53 operatively linked a promoter.

Curiel et al. teach a conditionally replicative recombinant adenovirus which (1) has a functional E1B-19k and (2) is E1B-55k-deleted or is E1A-deleted/modified and (3) comprises a therapeutic gene operatively linked to a promoter.

Curiel et al. does not teach that p53 is one of the therapeutic proteins. Rather, Curiel et al. uses thymidine kinase as an exemplary therapeutic gene.

However, Xu et al. teach that p53 is a therapeutic protein used to treat cancer. Xu is silent on the use of Adenovirus, since Xu et al. use plasmids to deliver p53. Xu et al. does not specifically state that the p53 is from humans, but this would be obvious to a skilled artisan, since human p53 is often used in anticancer methods.

Claim 27 is directed to the adenovirus of claim 26 wherein said adenovirus is a "human adenovirus." Curiel et al. teach the adenovirus is a chimeric human adenovirus comprised of subtypes 2 and 5 (claim 10).

Claim 28 is directed to the recombinant virus according to claim 26, wherein expression of at least one essential early adenovirus gene is controlled by a tumor specific promoter. Curiel et al. teach tumor specific control of E4 or E2 (col.10, lines 1-6).

Claim 29 is directed to the recombinant virus according to claim 26, wherein the adenovirus is a heterologously trans-complemented adenovirus. The specification uses a definition of "heterologously trans-complemented adenovirus" which is different from the usual meaning in the art. The specification teaches, "In a first type of

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replication competent recombinant adenovirus said parts that are essential for at least one step of the adenovirus infectious life cycle are also removed, but the essential functions of said parts are complemented by inserting functional expression cassettes for heterologous proteins that provide said essential functions in the recombinant adenovirus genome. This type of recombinant adenovirus is referred to herein as a heterologously trans-complemented adenovirus, and therefore is to be regarded as replication competent according to the definition presented herein.” (page 3, lines 3-12). In the adenovirus described by Curiel, replace endogenous viral E4 and/or E2 with a modified e\$ and/or E2 construct having tumor-specific expression (Examples 10-11). By the definition provided by the instant specification, the resulting adenovirus of Curiel is a heterologously trans-complemented adenovirus.

Claims 30-31 are directed to the adenovirus of claim 26 wherein the genome of said adenovirus comprises “E1B-55kDa protein” (claim 30) and “E1B-19kDa protein” (claim 31). Claim 32 is directed to the adenovirus of claim 30 wherein the genome of said adenovirus comprises “genes of the...E4 region.” Claim 33 is directed to the recombinant virus according to claim 30, where the virus genome comprises at least the gene encoding the adenovirus E4 or F6 protein or function analogues or derivative thereof. Curiel et al. describe a variety of conditionally replicative recombinant adenoviruses which satisfy the limitations of claims 30-33.

Claim 34 is directed to the adenovirus of claim 26 wherein a mutation in an E1A region encompassing at least part of the pRb-binding CR2 domain of E1A. Curiel et al teach a modified conditionally replicative recombinant adenovirus which contains a

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deletion of nucleotide sequences encoding the RB binding site of E1a (see Curiel claim 5).

Claim 35 is directed to the recombinant virus according to claim 26, wherein the restoring factor is p53 protein or a functional analogue or derivative thereof. Xu et al. teach p53.

Claim 38 is directed to the adenovirus of claim 26 wherein the target cell is a human cell chosen from the group consisting of cancer cells, arthritic cells, smooth muscle cells, and cells infected with a virus. Both references use cancer cells.

Claim 39 is directed to the adenovirus of claim 27 wherein said human adenovirus is a serotype 5 adenovirus. Curiel et al. teach the adenovirus is a chimeric human adenovirus comprised of subtypes 2 and 5 (claim 10).

Claim 40 is directed to the recombinant virus according to claim 34, wherein the mutation comprises a deletion encompassing amino acids 122-1129 (LTCHEAGF) of SEQ ID NO:5. Curiel et al. teach that E1a is deleted. A deletion encompassing amino acids 122-1129 (LTCHEAGF) of SEQ ID NO:5 is encompassed by deletion of E1a.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to substitute the particular anti-cancer protein, p53 (from Xu et al) in the conditionally replicative recombinant adenovirus of Curiel et al.

Regarding the rationale for combining prior art elements according to known methods to yield predictable results, all of the claimed elements were known in the prior art and one skilled in the art could have combined the element as claimed by known methods with no change in their respective functions, and the combination would have

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yielded predictable results to one of ordinary skill in the art at the time of the invention.

Each of the elements (conditionally replicative recombinant adenovirus with a functional E1B19 and the therapeutic gene p53) are taught Curiel or Xu and further they are shown to be used as in anti-cancer therapies. It would be therefore predictably obvious to use a combination of these elements in an adenovirus used for cancer therapy.

An artisan would have expected success, because the molecular biology required to substitute the p53 gene for the HSV-TK gene in the conditionally replicative recombinant adenovirus would be known to a skilled artisan.

The claimed invention is obvious. Curiel et al. teach a conditionally replicative recombinant adenovirus which (1) has a functional E1B-19k and (2) is E1B-55k-deleted or is E1A-deleted/modified and (3) comprises a therapeutic gene operatively linked to a promoter. Simply substituting one therapeutic gene for another (e.g., substituting p53 for HSV-TK) in an adenovirus shown to be effective in treating cancer would have been obvious to a skilled artisan. The molecular biology required to make this substitution is simple for a skilled molecular biologist. A skilled artisan would have found this simple substitution to be *prima facie* obvious.

Therefore the adenovirus as taught by Curiel et al in view of Xu et al would have been *prima facie* obvious over the adenovirus of the instant application.

Curiel, Xu & Lin

Claims 36-37 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US-6,824,771) in view of Xu et al. (Human Gene Therapy. 1997;

8:177-185) as applied to claims 26 and 35 above, and further in view of Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901) for the reasons of record and the comments below.

The applicant's arguments have been fully considered but are unpersuasive.

The applicant argues nothing in the disclosure of Lin et al. remedies the lack of reasonable expectation of success in combining conditionally replicating adenoviruses (of Curiel) with p53 (of Xu). As the applicant has not provided an explicit argument against the rejection of claims 36-37, the examiner refers the applicant to the discussion above (see Curiel & Xu). Accordingly, the examiner finds the applicant's argument unpersuasive.

Therefore, the examiner hereby maintains the rejection of claims 36-37 under 35 U.S.C. 103(a) as being unpatentable over Curiel et al. in view of Xu et al. as applied to claims 26 and 35 above, and further in view of Lin et al.

The examiner reiterates the pending rejection:

Claims 36-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US-6,824,771) in view of Xu et al. (Human Gene Therapy. 1997; 8:177-185) as applied to claims 26 and 35 above, and further in view of Lin et al. (Cancer Research. Oct 15, 2000. 60. p.5895-5901).

The teachings of Curiel and Xu are described above in the previous 35 USC 103(a) rejection. Together they suggest replication competent recombinant adenovirus comprising the gene for p53 operatively linked to a promoter, which also comprises either E1b-19k or E1b-55k. In addition, Xu et al. teach that p53 can be used as an anti-

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tumor therapeutic gene for treating breast cancer. Xu et al. administered a plasmid which expressed the gene for p53 to MDA-MB-435 human breast cancer cells which lack p53.

Curiel and Xu fail to teach the limitations of claims 36-37, directed to specific mutations in the p53 protein, such that p53 lacks a functional binding domain for a human Mdm2 protein (claim 36) and such that p53 has mutated amino acids Leu-14 and Phe-19 in the p53 binding domain for a human Mdm2 protein (claim 37).

However, Lin et al. teach a variant form of human p53 having mutated amino acids Leu-14 and Phe-19. Lin et al. teach this mutant form of human p53 lacks a functional binding domain for a human Mdm2 protein. Lin et al. teach that the p53 14/19 engineered p53 variant is particularly effect against human cancers that express abnormally high levels of Mdm2 oncogene product. MDA-MB-435 human breast cancer cells express high levels of Mdm2 oncogene product.

It would have been obvious to the person of ordinary skill in the art at the time of the invention was made to substitute the p53 14/19 engineered p53 variant of Lin et al. into the replication competent recombinant adenovirus comprising the gene for p53 operatively linked to a promoter, which also comprises either E1b-19k or E1b-55k as suggested by Curiel and Xu.

The person of ordinary skill in the art would have been motivated to substitute the p53 14/19 engineered p53 variant of Lin et al. into the replication competent recombinant adenovirus comprising the gene for p53 because the cancer cell type treated by Xu et al. (i.e., MDA-MB-435 human breast cancer cells) express high levels

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of Mdm2 oncogene product and Lin et al. suggests that tumor cells which express high levels of Mdm2 oncogene product are particularly well suited for anti-tumor treatment with substitute the p53 14/19 engineered p53 variant.

An artisan would have expected success, because the molecular biology required to modify a recombinant adenovirus was known and practiced in the art at the time of the invention.

Therefore the adenovirus as taught by Curiel, Xu & Lin would have been *prima facie* obvious over the adenovirus of the instant application.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

No claims are allowed.

Examiner Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Scott Long** whose telephone number is **571-272-9048**.

The examiner can normally be reached on Monday - Friday, 9am - 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Joseph Woitach** can be reached on **571-272-0739**. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SCOTT LONG/
Primary Examiner, Art Unit 1633